REMARKS

Claims 1-21 and 23-25 were pending prior to this response, with claims 1-20 and 23 being withdrawn pursuant to a restriction requirement. By the present communication, no claims are added or cancelled and claims 21 and 25 have been amended to describe Applicants' invention with greater particularity. The amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1-21 and 23-25 are currently pending with claims 1-20 and 23 being withdrawn.

The Declaration

The Examiner indicates that the Declaration filed herein is defective under 37 C.F.R. §1.67(a) for allegedly failing to include the serial number of the parent application. To correct this alleged defect, Applicants submit herewith a new Declaration that identifies the parent application by serial number. Applicants respectfully submit that the new Declaration meets all requirements under 37 C.F.R. §1.67(a).

Objection to the Drawings

The Office Action indicates that the drawings need correction for the reasons noted on Form PTO 948, namely improper left and right margins in Figure 3 and the presence of circles around numbers in Figures 1-3. To overcome the objection to the drawings, Applicants submit herewith formal drawings having correctly sized left and right margins in Figure 3 and lacking circles around numbers in Figures 1-3. In view of the corrected Figures 1-3 submitted herewith, Applicants respectfully request reconsideration and withdrawal of the objection to the drawings.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claim 25 on the grounds that the limitation "verifying in..." in line 1 lacks antecedent basis under 35 U.S.C. § 112, Second Paragraph. Applicant has changed the dependency of claim 25 from claim 23 to claim 24, thereby providing correct antecedent basis for the phrase "verifying in..." in claim 25 in accordance with the Examiner's assumption that Applicants intend that claim to depend from claim 24.

The Rejection Under 35 U.S.C. § 102(b)

Applicants respectfully traverse the rejection of claims 21 and 24 under 35 U.S.C. §102(b) as allegedly being anticipated by Jaroszeski *et al.* (1994) *Anal. Biochem.* 216:271-275 (hereinafter "Jaroszeski"). The invention methods for ex vivo introduction of at least one chromosome into a eukaryotic cell, wherein the cell is not a plant cell, as defined by claim 21, distinguishes over the disclosure of Jaroszeski by reciting "contacting at least one chromosome ex vivo substantially simultaneously with the application of an electric pulse to the cell under conditions sufficient to cause transformation of said cell with the at least one chromosome, wherein the at least one chromosome is a gene-bearing DNA/protein complex, a natural human chromosome, a mammalian chromosome, an artificial chromosome, or a yeast chromosome, and wherein said at least one chromosome is encapsulated in a liposome or a micelle." The Examiner asserts that "because the definition of "liposome micelle" has not been explicitly set forth by Applicant, the limitation has been given its broadest reasonable interpretation according to *Stedman's Medical Dictionary* definition of micelle, *Any water-soluble aggregate, spontaneously and reversibly, formed from amphiphile molecules*, to include biological

membranes" (Office Action, page 6). that the at least one chromosome is encapsulated in an artificial liposome or micelle. In fact, in framing the rejection of claim 21 over Jaroszeski, the Examiner has taken the terms "liposome" and "micelle" out of context in order to "equate" any wild type cell containing a chromosome with an artificial construct, i.e., at least one chromosome that has been artificially captured, or "encapsulated", in a manmade liposome or micelle.

Applicants respectfully submit that the phrase "encapsulated in a liposome or micelle," when read in context by those of skill in the art, would simply not be interpreted to include naturally occurring cells because the complete phrase has a meaning in the art that is so well understood that resort to a definition in a medical dictionary for the meaning of individual terms in the phrase would not be appropriate. In particular, the term "encapsulated" is routinely used in the art to mean that something is artificially encompassed and held within a manmade structure.

Jaroszeski fails to disclose a method for introducing at least one chromosome into a eukaryotic cell by artificially encapsulating the at least one chromosome in a liposome or micelle and then transforming the cell with the chromosome by application of an electric pulse thereto. Therefore, Applicants respectfully submit that Jaroszeski fails to disclose each and every element of the invention methods, as recited by claim 21, as would be required to support a rejection under 35 U.S.C. § 102(b). Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 103(a)

Applicants respectfully traverse the rejection of claims 23 and 24 under 35 U.S.C. 103(a) as allegedly being unpatentable over the combined disclosures of Strauss and Jaenisch (1992) 11:417-422 (hereinafter "Strauss and Jaenisch") and Chernomordik et al (1991) *Biochim Biophys. Acta* 1070:193-197 (hereinafter "Chernomordik"). Applicant respectfully submits that the invention methods of claims 23 and 24 (which depend from amended claim 21) require that the eukaryotic cell is "transformed" with the at least one chromosome that was encapsulated in the liposome or micelle. While Strauss and Jaenisch disclose that a cell can be transfected with YAC DNA at very low efficiency, the Strauss-Jaenisch method requires incubation of the YAC DNA in spermine for 36 to 48 hours as an "essential" precaution "to prevent the YAC against breakage during handling" (page 419, left column). Too little spermine resulted in fragmentation of the YAC and too much spermine resulted in "massive aggregation and precipitation of the YAC DNA" in the Strauss-Jaenisch method, which employed low ionic strength buffers for the transfection. Thus Strauss-Jaenisch neither teach nor suggest that an electroporating electric field could be used to improve the efficiency of chromosome transfer into the cells.

Applicants respectfully submit that Chernomordik fails to overcome the deficiencies of the disclosure of Strauss-Jaenisch for teaching or suggesting the invention methods. Chernomordik's method employs a liposome loaded with a fluorescent dye (a small relatively stable molecule), so fragmentation of the marker entity is not an issue. In view of these teachings regarding the fragility of chromosome-containing nucleic acid constructs by Strauss and Jaenisch, one of skill in the art would have no reasonable expectation that a liposome-

encapsulated YAK DNA or other large chromosome-containing construct could replace the dye in the electroporation-enhanced method of Chernomordik without fragmentation of the YAK DNA. Those of skill in the art might as well expect that rectangular pulses of electric field applied to the cells/liposome mixture would damage the chromosome(s) in view of Chernomordik's disclosure that the percentage of dead cells increases with the intensity of the electric field used in the method (page 194, right col.).

Moreover, Chernomordik fails to disclose that electric field treatment of the liposome-encapsulated fluorescent dye and cells results in the cells being "transformed" with the dye molecules. Instead, although Chernomordik's cells become "associated" with the dye, Chernomordik concludes after study of the data that :the electrostimulated increase of fluorescence associated with cells reflects the *binding* of intact liposomes onto the cell membranes. There is no suggestion by Chernomordik that the dye molecules are actually transferred from the liposomes to the interior of the cells.

Therefore, Applicants respectfully submit that *prima facie* obviousness of the invention methods for ex vivo introduction of at least one chromosome into a eukaryotic cell, as defined by amended claim 21 (and claims 24 and 25 dependent thereon), is not established over the Strauss-Jaenisch –Chernomordik combination of disclosures and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

In view of the above amendments and remarks, Applicants respectfully submit that all rejections of the pending claims have been overcome and passage of claims 21, 24 and 25 to allowance is respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosure: Exhibit A
New Declaration
Formal drawings – Figures 1-3

Applicants: Jay M. Short
Application No.: 08/858,616
Filed: May 15, 2001
Exhibit A: Page 1

EXHIBIT A

Version with Markings to Show Changes Made

In the Claims

Please amend claims 21 and 25 as follows:

21. (Twice Amended) A method for the ex vivo introduction of at least one chromosome into a eukaryotic cell, wherein said cell is not a plant cell, said method comprising contacting at least one chromosome ex vivo substantially simultaneously with the application of an electric pulse to the cell under conditions sufficient to cause [fusion] transformation of said [at least one chromosome and said] cell by said chromosome, wherein the at least one chromosome is a gene-bearing DNA/protein complex, a natural human chromosome, a mammalian chromosome, an artificial chromosome, or a yeast chromosome, and wherein said at least one chromosome is encapsulated in a liposome or micelle.

25. (Amended) The method of claim [23]24, wherein the verifying involves fluorescence activated cell sorting of the cells to obtain those that contain the at least one chromosome.